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CASE REPORT

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Successful pregnancy after ileal exclusion in progressive familial intrahepatic cholestasis type 2

Piotr Czubkowski, Irena Jankowska, Joanna Pawłowska

The Children's Memorial Health Institute, Department of Gastroenterology, Hepatology, Feeding Disorders and Pediatrics, Warsaw, Poland.

ABSTRACT

Progressive familial intrahepatic cholestasis type 2 (PFIC 2) results from mutations in ABCB11 gene coding bile salt export pump (BSEP). Medical treatment is usually unsuccessful and surgery intervention is necessary. Partial external biliary diversion (PEBD) is regarded as the first choice of surgical treatment. Ileal exclusion (IE) is an alternative operation if external stoma is not tolerated; however, a favorable outcome is uncertain. In chronic liver diseases pregnancy brings additional risk of deterioration of liver function and generally is not recommended. We present the first case report of successful pregnancy in a genetically confirmed PFIC 2 patient after surgical conversion from PEBD to IE.

Key words. Partial external biliary diversion. Quality of life. Maternity. External stoma. Bile acids.

INTRODUCTION

Progressive familial intrahepatic cholestasis type 2 (PFIC2) results from mutations in *ABCB11* gene coding bile salt export pump (BSEP), which is the major transporter of bile acids from hepatocytes into bile in humans and is genetically and phenotypically distinguished from PFIC-1.[1] BSEP deficiency is also associated with benign recurrent intrahepatic cholestasis type 2 (BRIC-2), and genetic polymorphisms are linked to intrahepatic cholestasis of pregnancy (ICP) as well.[2]

In PFIC-2, a medical approach is usually disappointing, and if not treated surgically, patients usually develop end-stage liver disease before adolescence. Surgical interventions aim at interfering with the enterohepatic circulation of bile salts. Partial external biliary diversion (PEBD), in which the jejunal conduit between the gallbladder and external stoma is created, is the treatment of choice in noncirrhotic patients if medical therapy fails.[3-5] Usually it is well tolerated; however, in some patients permanent stoma is not acceptable due to esthetic and psychological issues. Ileal exclusion (IE) is an alternative operation in which the distal 15% of the small bowel is bypassed by ileocolonic anastomosis, but this operation should be offered with caution since long-term outcomes remain uncertain.[5,6]

We present the first case report of successful pregnancy in a genetically confirmed PFIC-2 patient after surgical conversion from PEBD to IE.

CASE REPORT

We present the case of a currently 30-year-old woman, who had been admitted to our hospital at the age of 12 years because of severe pruritus without jaundice and short stature. Liver function tests showed high bile acids (BA) concentration and low GGTP activity. Genetic testing toward PFIC type 1 and 2 was performed in *ATP8B1* and *ABCB11* genes, respectively. PFIC-2 was confirmed by C.1445 A > G; p.Asp482Gly (HOM) mutation in *ABCB11* gene, which is characteristic for the Polish population of patients.[1] No mutations were found in *ATP8B1*. After treatment with ursodeoxycholic acid (UDCA) 20 mg/kg/d, we observed a significant decrease in BA concentration from 269 μmol/l to 30 μmol/l; however, there was no effect on severity of pruritus. At the age of 14 she underwent successful PEBD with complete relief of pruritus and normalization of bile acids afterwards. For the next four

Correspondence and reprint request: Piotr Czubkowski, MD, PhD.
The Children's Memorial Health Institute
Department of Gastroenterology, Hepatology and Feeding Disorders
Al. Dzieci Polskich 20, 04-730 Warsaw, Poland
Tel. +48228157384 Fax +48228157382
E-mail: piotr.czubkowski@mp.pl

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years she tolerated stoma well with neither medical nor psychological issues. Subsequently her mental state progressively deteriorated. Initially she avoided contact with classmates and peers, regressed at school, and finally developed severe depression necessitating a complex psychiatric approach. In spite of intensification of psychological support and modification of psychiatric treatment her mental state did not improve. At the age of 21 she underwent stoma closure and IE according to the previously described technic.[5] The intraoperative liver biopsy showed normal liver architecture, without fibrosis, cholestasis, or inflammation. Within the first months after operation we observed recurrence of pruritus accompanied by increased BA (144 μmol/l). UDCA was again administered (20 mg/kg/d) with laboratory and clinical improvement. There was no pathology in control liver biopsy one year after IE.

In terms of mental state, we observed permanent regression of psychiatric symptoms and all antidepressants were withdrawn. After another four years at the age of 25 the patient became pregnant (no consanguineous parents).

After an uneventful six months, in the third trimester she developed pruritus with increased BA (66.2 μmol/l) and moderate coagulopathy (INR 2.5), which was well controlled on vitamin K supplementation. The other liver function tests remained within normal ranges. There was no expected response to UDCA treatment (15 mg/kg/d) but eventually the severity of pruritus gradually decreased and resolved two months after delivery with no relapse to date.

In the 38th week of pregnancy a female neonate was born with weight 3,220 g, 33 cm height, and 10 Apgar points. There were no complications during the newborn period and laboratory tests remained within normal ranges (bilirubin, BA, ALT, AST). Currently, the child is 5 years old and does not present any symptom of cholestasis. The mother is under regular outpatient check-ups and currently is doing well, with stable liver function and no pruritus in five-year follow-up after pregnancy.

DISCUSSION

The quality of life in PFIC-2 is influenced by the state of liver function, severity of pruritus, physical development, and psychological problems related with permanent external stoma after PEBD. Moreover, in young women the maternal instinct may bring additional pregnancy-related problems. In our report we described two important issues, successful conversion from PEBD to IE, followed by pregnancy in an PFIC-2 patient.

PEBD is the treatment of choice in noncirrhotic PFIC patients if medical treatment is unsuccessful. IE is an alternative option but should be reserved only for patients who cannot benefit from PEBD, but only after weighing all the pros and cons, taking into account the eventual risk of disease progression.[4-6] In our case the main problem was severe psychological deterioration due to stoma esthetical intolerance, which gradually worsened during adolescence period. The patient's quality of life was significantly disturbed, and that was the main reason for the decision of stoma closure. In spite of transient relapse of pruritus, her overall psychological state significantly improved, which outlines the importance of esthetic issues in adolescence. Interestingly, UDCA therapy was successful after IE, contrary to its failure before PEBD. Whether the relief of pruritus resulted from pharmacological drug effect, milder form of cholestasis, or adaptation to increased overall pool of bile salts after IE remains unclear. Afterwards, the patient became pregnant and to date it is the first reported case in genetically confirmed PFIC-2, demonstrating the possibility of successful gestation and delivery in this rare disorder. Three successful pregnancies were reported previously in PFIC-1, although in this type the genetic background and clinical manifestation is different from PFIC-2. Two women developed significant pruritus during gestation and required repeated sessions of plasmapheresis, with good clinical outcome.[7,8] One patient with PFIC-1 after liver transplantation developed LFT abnormalities during pregnancy, with no pruritus and with good response to oral steroids (liver biopsy was not performed).[9]

In general, maternity in chronic liver disorders is not recommended since it is difficult to estimate the risk of sudden deterioration of liver function. In the presented case, in spite of long-lasting stable liver function, the patient developed cholestasis and coagulopathy, probably originating from hormonal changes during pregnancy, but the exact mechanisms remain unclear. Several estrogens and progesterone metabolites are able to induce trans-inhibition of BSEP and the subsequent toxicity induced by the accumulation of bile acids, which may also play a role in the etiopathogenesis of intrahepatic cholestasis of pregnancy (ICP).[10,11] Mutations in MDR3 (ABCB4) gene coding transporter for phospholipids across the canalicular membrane may account for 15% of cases of ICP.[12] Interestingly, a

few "common" BSEP mutations (including p.E297G, p.D482G, and p.N591S) have been detected in ICP-patients in heterozygous form, and common BSEP polymorphism (p.V444A) has been linked to ICP as well.[13] The reoccurrence of BSEP cholestasis and development of ICP may be clinically indistinguishable, since both usually present with pruritus, elevated bile acids and aminotransferases, and normal hepatic imaging.[11,12] Moreover, in ICP, mutations or polymorphisms of some hepatobiliary transport proteins may contribute to disease pathogenesis or severity, but on the other hand consideration must be given to the possibility of other rare underlying hepatic disorders that may be unmasked during pregnancy with cholestasis as its first manifestation.[14] Thus, the diagnosis of ICP should be given after exclusion of preexisting liver disease.[15]

Pruritus remains the most important clinical symptom of PFIC-2. With poor response to medical treatment, surgical interventions including liver transplantation are the mainstay of current management. Recently, a new therapeutic option has emerged for PFIC-2. Mutation-specific chaperone therapy with 4-phenylbutyrate was shown to improve liver function and relieve pruritus in patients with PFIC-2, which probably relied on the mistrafficking of BSEP mutant, resulting in an increased cell-surface expression.[16,17]

In summary, this case underlines the importance of continuous evaluation of psychological issues in patients with permanent external stoma, especially in adolescence. In PFIC-2, pregnancy options should be presented very cautiously with regard to possible deterioration of liver function and reoccurrence of pruritus. In our opinion, the liver biopsy before final decision may give some clues, but practically estimation of functional hepatic reserve is not possible. Pregnant women with PFIC-2 should remain under close follow-up provided by an obstetrician and hepatologist.

ABBREVIATIONS

- **ICP:** intrahepatic cholestasis of pregnancy.
- **IE:** ileal exclusion.
- **PEBD:** partial external biliary diversion.
- **PFIC:** progressive familial intrahepatic cholestasis.
- **BSEP:** bile salt export pump.
- **UDCA:** ursodeoxycholic acid.

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